## REMARKS

The examiner and her supervisor, Lorraine Spector, are thanked for their consideration in participating in a telephonic conference regarding this case on October 29, 2003. Claims 36-38 and 42-52 presently are pending in the application and stand rejected under 35 U.S.C. § 112 or 102(e) or both. New claims 53-63 have been added to the application. The applicant believes that new claims 53-63 raise no new issues of patentability and asks that they be entered into the application. In addition, claims 36, 38 and 42 have been amended as shown above, and claims 50-52 have been cancelled.

In addition to rejecting the claims, the examiner has objected to the amendment to the specification that was submitted on July 8, 2003. As indicated above, the specification has been further amended as suggested by the examiner in order to obviate this objection.

Claim 36 has been amended so that instead of reciting an "antibody that specifically binds" human RANKL, it refers now to antibodies that bind with higher affinity to human RANKL than to murine RANKL. Claim 42 has been amended similarly to recite antibodies that bind with higher affinity to recited subportions of human RANKL than to murine RANKL. Similar limitations are also present in newly added independent claims 62 and 63. The amendments to claims 36 and 42 and new claims 62 and 63 are supported by the application for the following reasons.

As was noted in the amendment of July 8, 2003, by the time this application was filed, antibodies had been reported that were capable of differentiating between two proteins that differed by only one amino acid (see, for example, Lederman et al., *Mol Immunol* 28(11):1171-1181 (1991), and Abaza and Atassi, *J Prot Chem* 11(5):433-444 (1992); copies were provided as Exhibits C and D in the amendment of July 8, 2003). The present specification discloses the amino acid sequences for both human RANKL (SEQ ID NO:13) and murine RANKL (SEQ ID NO:11), which differ at 16% of their amino acid sequences (see page 26, lines 35-36). Example 10 of this application furthermore provides a method for preparing antibodies using RANKL as the immunogen

(pages 27-28); other methods for preparing such antibodies were known in the art. The application teaches also that RANKL bound to a solid substrate can serve as an affinity reagent to selectively bind antibodies raised against the same or a different RANKL protein (page 4, line 36 to page 5, line 2). Clearly, such disclosure contemplates antibodies that bind with higher affinity to one form of RANKL than to another. Given the teachings of the present application and the knowledge of one skilled in the art at the time the application was filed, it is believed that the amendments to claims 36 and 42 and the similar limitation in new claim 63 are adequately supported. New claim 62, which covers antibodies that bind human but not mouse RANKL, is supported also by the disclosure of mouse and human RANKL and methods of making antibodies. The antibodies of new claim 63 are further limited by being made by immunizing with a portion of the human RANKL protein, as supported in the application, for example, at page 5, lines 27-33 and in Example 10, pages 27-28. Accordingly, the amendments to claims 36 and 42 and new claims 62 and 63 do not constitute the addition of new matter to the application.

Claim 38 has been amended by deleting portions of the preamble that are believed to be non-essential for delineating the invention set forth in this claim. Claim 38 has been amended further by replacing the word "preparing" with the word "generating." Use of the word "generating" is supported in the specification, for example, in Example 10, e.g., page 27, lines 27-29). This change was made to better express the intended meaning of this claim and it is believed to neither broaden nor narrow the scope of claim 38. In addition, part g) has been cancelled from claim 38. These amendments do not constitute the addition of new matter to the application.

Claims 50-52 are cancelled without prejudice.

New claims 53-58 depend from claim 38 and each of these new claims recites one member of the Markush group of claim 38. Thus, these new claims do not constitute the addition of new matter to the application.

New claims 59 and 60 describe methods for using cloned hybridoma cells to produce the monoclonal antibodies of claim 37, while new claim 61 describes a cloned hybridoma cell that produces a monoclonal antibody according to claim 37. New

claims 59-61 are supported in the application, for example, in Example 10 (pages 27-28). Thus, new claims 59-61 do not constitute the addition of new matter to the application.

The examiner is respectfully requested to reconsider the rejections and objection set forth in the Office Action of October 2, 2003 in view of the amendments shown above and the comments that follow.

**Objection to the Specification**

The examiner has objected to a previous amendment to the specification but indicated that the objection would be withdrawn if the wording of the amendment was changed as suggested in the Office Action of October 2, 2003. As shown above, the suggested change has been made. The examiner therefore is respectfully requested to remove the objection to the specification.

**Rejections under 35 U.S.C. § 112, Second Paragraph**

Claims 36, 37 and 42-52 stand rejected under 35 U.S.C. § 112, second paragraph. It is believed that the examiner meant to include claim 38 in this rejection. The basis for this rejection is that independent claims 36 and 42 pertain to antibodies that "specifically bind," while independent claims 38 and 50 refer to antibodies that "bind" the target. The examiner has indicated that this rejection would be overcome if consistent language were used, i.e., if claims 38 and 50 were amended to read "specifically binds."

Amended claims 36 and 42 no longer include the term "specifically binds," but instead recite antibodies that bind with higher affinity to human RANKL than to mouse RANKL. By reciting both target antigen and test antigen, the claimed antibodies' specificity is explicitly defined, thus there is no need to include "specifically" in these claims. Accordingly, this ground of rejection is now moot as applied to claims 36, 42 or claims depending therefrom, i.e., claims 37 and 42-49. Moreover, the preamble of claim 38 has been amended to eliminate language referring to antibody binding, thus this ground for rejection is moot with respect to this claim. Claims 50-52 have been cancelled, thus this rejection is moot also with respect to these claims. In view of these amendments, the examiner's concern regarding "binds" versus "specifically binds" is believed to be resolved and she is asked therefore to withdraw the rejections of pending claims 36-38 and 42-49 under 35 U.S.C. § 112, second paragraph.

## Rejections under 35 U.S.C. § 102(e)

Claims 36, 37 and 42-49 stand rejected under 35 U.S.C. § 102(e) over U.S. Patent No. 6,242,586 (Gorman et al.). Gorman et al. discloses the sequence of murine RANKL and describes antibodies to this protein. The examiner has noted that antibodies made using mouse RANKL as an immunogen might cross-react with human RANKL, and because of this has asserted that the present claims are anticipated by this reference.

To better differentiate the claimed antibodies from those taught by Gorman et al., claims 36 and 42 have been amended to state explicitly that the claimed antibodies bind with higher affinity to human RANKL than to mouse RANKL. Gorman et al. does not disclose human RANKL nor does it teach how to make antibodies that preferentially bind human RANKL. Accordingly, this reference does not anticipate the invention claimed herein (see, for example, *Elan Pharmaceuticals v Mayo Foundation*, 68 USPQ2d 1373, at 1375-1376 (Fed. Cir. Oct. 2003), restating previous holdings that in order to anticipate, a reference must provide sufficient disclosure to enable those skilled in the art to make the claimed invention without undue experimentation; copy enclosed).

In view of the amendments to the claims and the above comments, it is believed that claims 36 and 42, as amended, and claims 37 and 43-49 depending therefrom are not anticipated nor rendered obvious by Gorman et al. Accordingly, the examiner is respectfully requested to withdraw the rejection of claims 36, 37 and 42-49 under 35 U.S.C. § 102(e).

## Change of Inventorship

On January 24, 2003, the applicant submitted a Petition for Change of Inventorship. The examiner is kindly requested to take action on this petition.

## CONCLUSION

Claims 36-38, 42-49 and 53-63 now are pending in the application. In view of the above remarks and amendments, these claims are believed to be in condition for allowance. Notification to this effect is respectfully requested. If the examiner has any

further concerns regarding this application, she is urged to contact the undersigned at her direct dial phone number given below.

Respectfully submitted,

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FULL TEXT OF CASES (USPQ2D)
Cases Publishing the Week of Nov 03, 2003
Elan Pharmaceuticals Inc. v. Mayo Foundation for Medical Education and Research, 68 USPQ2d 1373 (CA FC

Elan Pharmaceuticals Inc. v. Mayo Foundation for Medical Education and Research, 68 USPQ2d 1373 (CA FC 2003)

# 68 USPQ2D 1373
# Elan Pharmaceuticals Inc. v. Mayo Foundation for Medical Education and Research
# U.S. Court of Appeals Federal Circuit

**No. 00-1467**
**Decided October 2, 2003**

## Headnotes

**PATENTS**

**[1] Patentability/Validity — Anticipation — Prior art (§115.0703)**

**Patentability/Validity — Specification — Enablement (§115.1105)**

Disclosure of assertedly anticipating prior art reference must be adequate to enable possession of desired subject matter, and reference that names or describes desired subject matter thus does not anticipate if subject matter cannot be produced without undue experimentation; in present case, summary judgment



that patents for transgenic animals harboring amyloid precursor protein allele having "Swedish mutation" are anticipated by prior art reference must be vacated and remanded for determination of whether reference enabled persons of ordinary skill in field of invention to make desired transgenic mouse without undue experimentation, since federal district court did not directly address question of enablement, which was not subject of summary judgment motion.

## Particular Patents

**Particular patents — Chemical — Transgenic animals**

5,612,486, McConlogue and Zhao, transgenic animals harboring APP allele having Swedish mutation, summary judgment of invalidity reversed.

5,850,003, McConlogue and Zhao, transgenic rodents harboring APP allele having Swedish mutation, summary judgment of invalidity reversed.

**Case History and Disposition**
Appeal from the U.S. District Court for the Northern District of California, Alsup, J.

Action by Elan Pharmaceuticals Inc. and Athena Neurosciences Inc. against Mayo Foundation for Medical Education and Research for patent infringement. Plaintiffs appealed from summary judgment holding patents in suit invalid for anticipation. Initial opinion on appeal (64 USPQ2d 1292) was vacated, and is replaced with present opinion. Summary judgment of invalidity reversed and remanded.

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**Judge:**
Before Newman, Gajarsa, and Dyk, circuit judges.

## Opinion Text

**Opinion By:**
Newman, J.

The initial opinion in this appeal, reported at *Elan Pharmaceuticals, Inc. v. Mayo Foundation*, 304 F.3d 1221, 64 USPQ2d 1292 (Fed. Cir. 2002), has been vacated, 314 F.3d 1299 (Fed. Cir. 2002) (*en banc*) and is replaced with this opinion and decision.

The United States District Court for the Northern District of California, granting the Mayo Foundation's motion for summary judgment of patent invalidity, held that Elan's two patents in suit, United States Patent No. 5,612,486 (the '486 patent) for "Transgenic Animals Harboring APP Allele Having Swedish Mutation," and Patent No. 5,850,003 (the '003 patent) for "Transgenic Rodents Harboring APP Allele Having Swedish Mutation,"are invalid on the ground of anticipation by United States Patent No. 5,455,169 entitled "Nucleic Acids for Diagnosing and Modeling Alzheimer's Disease" (the Mullan reference).1

In response to the questions raised in the petitions for reconsideration, we clarify that invalidity based on anticipation requires that the assertedly anticipating disclosure enabled the subject matter of the reference and thus of the patented invention without undue experimentation. Applying this rule, we remand for determination of whether the Mullan reference was an enabling disclosure. The summary judgment is reversed, and the case is remanded for further proceedings.

## BACKGROUND

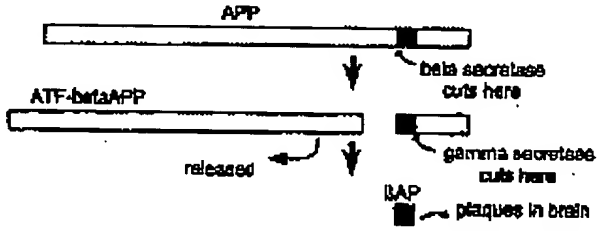
At the time of the Elan invention it was known that the brains of people with Alzheimer's disease contain abnormal tangles and deposits of plaques, and that a principal component of the plaques is a protein fragment called beta-amyloid peptide or betaAP (also designated bAP and Ab). The formation of betaAP in brain tissue is believed to induce or foster formation of Alzheimer's disease plaques.

It is believed that a mechanism by which betaAP is formed is the abnormal cleavage of a protein produced in brain cells, called the amyloid precursor protein (APP); and that this abnormal cleavage occurs when an enzyme produced in the brain, called beta-secretase, cleaves the APP molecule between amino acids 596 and 597; and a second enzyme produced

Page 1375

in the brain, called gamma-secretase, releases the betaAP fragment from a portion of the cleaved APP. The mechanism is illustrated in the Elan brief as follows:

**Fig.1 - Processing of APP to BAP and ATF-betaAPP**




Humans who do not develop Alzheimer's disease are believed to break down the APP in a manner that does not form significant amounts of betaAP in the brain.

The Swedish mutation is an abnormal gene 2 that was discovered on chromosome 21 in a Swedish family that has an unusually high incidence of early-onset Alzheimer's disease. This mutation is described in the Mullan patent as a variation in the DNA nucleotides that encode codons 670 and 671,3 wherein lysine and methionine, the amino acids normally encoded at these positions, are replaced with asparagine and leucine.

The Elan patents are directed to transgenic rodents whose genetic makeup has been modified to include the Swedish mutation. Claim 1 of the '486 patent is representative:

1. A transgenic rodent comprising

a diploid genome comprising a transgene encoding a heterologous APP polypeptide having the Swedish mutation wherein the amino acid residues at positions corresponding to positions 595 and 596 in human APP695 are asparagine and leucine, respectively,

wherein the transgene is expressed to produce a human APP polypeptide having the Swedish mutation,

and wherein said polypeptide is processed to ATF-betaAPP in a sufficient amount to be detectable in a brain homogenate of said transgenic rodent. Dependent claims add the limitations that the rodent is murine (mouse) and that the transgene is nonhomologously integrated.

The claims of the '003 patent differ only in that they include a promoter and a polyadenylation site. Claim 1 is representative:

1. A transgenic rodent comprising

a diploid genome comprising a transgene comprising in operable linkage a promoter, a DNA segment encoding a heterologous APP polypeptide and a polyadenlyation site,

wherein the APP polypeptide has the Swedish mutation whereby the amino acid residues at positions corresponding to positions 595 and 596 in human APP695 are asparagine and leucine, respectively,

wherein the transgene is expressed to produce a human APP polypeptide having the Swedish mutation,

and wherein said polypeptide is processed to ATF-betaAPP in a sufficient amount to be detectable in a brain homogenate of said transgenic rodent. The Mullan reference was cited as prior art in prosecution of the Elan patents, and was distinguished upon amendment of the Elan claims to include the claim clause that refers to production of ATF-betaAPP in detectable amounts in the rodent brain.

The district court, granting Mayo's motion for summary judgment, held that the Mullan reference anticipates the Elan invention. Whether an invention is anticipated is a question of fact. *Hoover Group, Inc. v. Custom Metalcraft, Inc.*, 66 F.3d 299, 302, 36 USPQ2d 1101, 1103 (Fed. Cir. 1995). On appeal, Elan requests review of the district court's determination that the Mullan reference anticipates the claims of the Elan patent because the Elan mouse is inherent in Mullan. We conclude that Elan's arguments are more properly characterized as enablement arguments rather than inherency arguments.

To serve as an anticipating reference, the reference must enable that which it is asserted to anticipate. "A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art



are not enabled." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003). *See Bristol-Myers Squibb v. Ben Venue Laboratories, Inc.*, 246 F.3d 1368, 1374, 58 USPQ2d 1508, 1512 (Fed. Cir. 2001) ("To anticipate the reference must also enable one of skill in the art to make and use the claimed invention."); *PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter."). Review of Elan's opposition to Mayo's motion for summary judgment shows that, while Elan purports to contest Mayo's motion on the grounds that the Mullan patent does not inherently anticipate the Elan claimed mouse, the language and factual basis of this argument encompass enablement.

Enablement requires that "the prior art reference must teach one of ordinary skill in the art to make or carry out the claimed invention without undue experimentation." *Minnesota Mining and Manufacturing Co. v. Chemque, Inc.*, 303 F.3d 1294, 1301, 64 USPQ2d 1270, 1278 (Fed. Cir. 2002); *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1369, 52 USPQ2d 1129, 1134 (Fed. Cir. 1999) ("Whether undue experimentation would have been required to make and use an invention, and thus whether a disclosure is enabling under 35 U.S.C. §112, ¶ 1, is a question of law that we review de novo, based on underlying factual inquiries that we review for clear error.").

The factual premises of the enablement analysis for biological processes were addressed in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), the court explaining that determination of whether the requisite amount of experimentation is undue may include consideration of:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737; 8 USPQ2d at 1404. *See Amgen, Inc. v. Chugai Pharm. Co.*, 727 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (discussing application of the *Wands* factors). In *In re Goodman*, 11 F.3d 1046, 1052, 29 USPQ2d 2010, 2015 (Fed. Cir. 1993) the *Wands* factors were applied to a gene transformation method, the court finding that the method "would have required extensive experimentation that would preclude patentability."

[1] The disclosure in an assertedly anticipating reference must be adequate to enable possession of the

desired subject matter. It is insufficient to name or describe the desired subject matter, if it cannot be produced without undue experimentation. The principles underlying application of the criteria of enablement to the content of the prior art were discussed in *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985):

> It is well settled that prior art under 35 U.S.C. §102(b) must sufficiently describe the claimed invention to have placed the public in possession of it. Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his own knowledge to make the claimed invention. Accordingly, even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it is not enabling. It is not, however, necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the enablement requirement. *Id.* at 533, 226 USPQ at 621. *See also In re Borst*, 345 F.2d 851, 855, 145 USPQ 554, 557 (CCPA 1962) ("the disclosure must be such as will give possession of the invention to the person of ordinary skill. Even the act of publication or the fiction of constructive reduction to practice will not suffice if the disclosure does not meet this standard.").

The determination of what level of experimentation is "undue," so as to render a disclosure non-enabling, is made from the viewpoint of persons experienced in the field of the invention. *See Enzo Biochem*, 188 F.3d at 1373-74 (discussing evidence of enablement and nonenablement in an unpredictable field of biotechnology). "The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art." *In re Wands*, 858 F.2d 731, 737 [8



USPQ2d 1400] (Fed. Cir. 1988). In *Wands* the court observed that "[t]he test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed ...." *Id.*, *quoting In re Jackson*, 217 USPQ 804, 817 (Bd. App. 1982).

The Mullan reference contains an extensive description of the Swedish mutated gene, its source, the nature of the mutation, and its role in Alzheimer's disease. The reference also states that the invention provides a transgenic animal whose cells contain the mutated gene and express the Swedish mutated protein:

> The invention also provides a transgenic non-human animal containing, in a germ or somatic cell, the mutated nucleic acid of the invention, wherein the animal expresses a human amyloid precursor protein or fragment thereof which encodes an amino acid other than lysine at codon 670 and/or an amino acid other than methionine at codon 671. Mullan, col. 4, lines 35-40. Elan argues that the Mullan reference does not show all of the limitations of the Elan claims and does not enable the transgenic animal it describes. Elan stresses the uncertainty and difficulty of producing a transgenic animal, and argues that although Mullan foresaw a transgenic mouse and presented a compilation of known methods of gene transfer, the reference does not teach or suggest which method might succeed in creating the desired mutated mouse. Mayo in turn stresses the comprehensiveness of the Mullan disclosure, and that Elan indeed eventually succeeded with one of the methods mentioned by Mullan, using the Swedish gene discovered by Mullan and a mouse species recited by Mullan.

The Mullan reference summarizes the various known gene transfer techniques, with citations to scientific literature describing these techniques. The following extract is illustrative:

> One approach to creating transgenic animals is to target a mutation to the desired gene by homologous recombination in an embryonic stem (ES) cell line in vitro followed by microinjection of the modified ES cell line into a host blastocyst and subsequent incubation in a foster mother (see

Frohman and Martin, *Cell* (1989) 56:145). Alternatively, the technique of microinjection of the mutated gene, or a portion thereof, into a onecell embryo followed by incubation in a foster mother can be used. Certain possibilities for the general use of transgenic animals, particularly transgenic animals that express a wildtype APP fragment, are disclosed in Wirak et al., the *EMBO Journal*, 10(2) 289296 (1991); Schilling et al., *Gene* 98(2) 225230 (1991); Quon, et al. (1991) *Nature* 352:239; Wirak, et al. (1991) *Science* 253:323; and Kawabata, et al. (1991) *Nature* 354:476. Alternatively, viral vectors, *e.g.*, Adenoassociated virus, can be used to deliver the mutated gene to the stem cell. In addition, such viral vectors can be used to deliver the mutated gene to a developed animal and then used to screen (Mendelson et al., *Virology* 166:154165; Wondisford et al. (1988) *Molec. Endocrinol.* 2:3239 (1988)). Mullan, col. 11, line 58 to col. 12, line 11. Mullan states that site-directed mutagenesis can also be used, preferably so as to produce the desired mutation. The Mullan reference also names various known cloning vectors for creation of transgenic animals, and states that the vector is "selected based on the size of the desired insert and the ability to produce stable chromosome integration." The Mullan reference contains additional information, with citations to scientific articles and textbooks, proposing how vectors "can be constructed," the transgene "can be injected," and like statements.

Elan stresses that Mullan does not suggest which, if any, of the methods and vectors he cites might reasonably be predicted to succeed in producing a mouse operatively harboring the Swedish mutation. As explained in *Enzo Biochem*, 188 F.3d at 1372, "an enablement determination is made retrospectively, *i.e.*, by looking back to the filing date of the patent application and determining whether undue experimentation would have been required to make and use the claimed invention at that time." Thus the enablement of the Mullan and Elan mice would be determined separately.

The issue is not whether the Mullan teachings are an accurate compilation of the state of the scientific art at that time, and they are not challenged on that ground. The issue is whether his teachings enabled a person of ordinary



skill, without undue experimentation, to produce the desired transgenic mouse. The district court did not directly address the question of enablement, which was not the subject of the summary judgment motion.

Thus we remand for determination by the district court, upon consideration of relevant evidence and upon application of the law to the facts of this case, of whether the Mullan reference enabled persons of ordinary skill in the field of the invention to make the desired mutated mouse without undue experimentation.

*II*

This appeal was directed to the summary judgment that was granted on the ground of anticipation. Mayo's other defenses of invalidity, and the question of infringement, were not reached by the district court. Mayo's argument that the claims are invalid under §103 and/or §112, particularly if construed to have the breadth that Elan ascribes to them in order to reach the Mayo mouse, and any other issues properly raised, remain for consideration on remand.

*REVERSED AND REMANDED*

**Footnotes**

1 *Elan Pharmaceuticals, Inc. v. Mayo Foundation for Medical Education &Research*, 175 F.Supp.2d 1209 (N.D. Cal. 2000).

2 A gene is a segment of DNA that encodes for and leads to the production, through several complex steps, of the sequence of amino acids that constitutes a protein. A mutation is a change in the gene DNA and the changes in the ensuing products. *See* Bruce Alberts et al., *Essential Cell Biology* (1998), Ch.6 "DNA," Ch.7 "From DNA to Protein."

3 The positions at codons 670/671 (Mullan) and codons 596/597 (Elan) are the same, due to differing starting points in the APP chain. *See* '486 patent, col. 11, lines 29-34.

**- End of Case -**

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